PATENT

REMARKS

Entry of the Amendment, reexamination and further and favorable reconsideration of the subject application in light of the following remarks are respectfully requested.

1. Status of the Claims

Claims 54-62, 64-68, 70-73, 76, and 78-98 are pending. Claims 54-62, 64-68, 70-73, 76, 78-81, 94-96, and 98 stand rejected. Claims 82, 83, and 97 stand objected to. Claims 82 and 83 are allowable but for depending from a rejected claim. Claims 1-56, 63, 69, 74, 75, and 77 stand canceled.

Claims 84-93 are withdrawn. The Office incorrectly lists at least claim 93 as being withdrawn. Claim 93 refers to SEQ ID NO: 20. The Office alleged in the Office Action mailed July 13, 2006, that claim 93 is drawn to non-elected subject matter. Applicants elected SEQ ID NO: 20 for search purposes, so the claim encompasses the elected species. Applicants accordingly indicate the status of claim 93 as "Previously Presented" instead of "Withdrawn."

2. Support for the Amendments

Claims 54, 72, and 98 are amended to add Sequence Identifier Numbers. Claims 54 and 72 are further amended to recite an inherent property of the protein of interest in subsection (q), namely that the Lys at position 34 of GLP-1 is substituted with Arg.

To expedite prosecution, claims 70, 71, and 92 are amended to depend from pending claim 68 instead of canceled claim 69. Claims 64, 65, and 66 are amended to depend from claim 54 instead of canceled claim 63. Claim 66 is amended to delete recitation of the inherent property "having insulinotropic activity," which phrase had antecedent basis in claim 63.

The amendments do not introduce prohibited new matter. Applicants reserve the right to file a continuation or divisional application on any subject matter canceled by way of amendment, which have been made without disclaimer of or prejudice to the canceled subject matter.

3. Information Disclosure Statements

Applicants note with appreciation the acknowledgement of the Information Disclosure Statements filed September 15, 2003 and October 25, 2007.

The Examiner did not consider CH 1167155 listed on the IDS filed September 15, 2003, because a concise explanation of the reference was not provided. The English language abstract of CN 1167155 is accordingly provided in **Exhibit 1**. CN 1167155 is listed on a PTO Form 1449, provided as a courtesy in Exhibit 1. No fee is believed due, because the reference was already listed on an Information Disclosure Statement.

4. Continued Examination under 37 C.F.R. § 1.114

Applicants note that the Request for Continued Examination (RCE) of the subject application stands accepted.

5. Objections to the Claims

Claims 54-62, 64-68, 72, 73, 76, 78-81, and 98 stand objected to because they fail to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 (Sequence Rules). Applicants amend the claims to recite Sequence Identifier Numbers, mooting the rejection.

The Office objects to claim 97 for allegedly "reciting the genera of protective peptides, helper peptides, and peptides of interest, whereas the claim is limited to the specific sequences of SEQ ID NOS: 23-23 that contain the specific protective peptide, helper peptide, and peptide of interest." Applicants traverse the objection.

The Office alleges that a claim is improper in form if it both recites a genus and specifically recites various species within the genus in a "wherein" clause. The Office is mistaken. The Office has authority to object to the form a claim only under 37 C.F.R. § 1.75(a)-(i). None of the subsections of 37 C.F.R. § 1.75 pertains to the present issue. Claim 97 complies with all the relevant subsections of 37 C.F.R. § 1.75(a)-(i), and the objection accordingly should be withdrawn. If the Office maintains this objection, the Office is requested to provide (in a non-final Office Action) specific authority within one of the subsections of 37 C.F.R. § 1.75 and reasons supporting the objection.

6. Rejection under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 54-62- 64-68, 72, 73, 76, 78-81, 94-96, and 98 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that allegedly is inadequately described in the specification. Applicants respectfully traverse the rejection.

The Office maintains the rejection, because the specification allegedly inadequately describes a "helper peptide." Specifically, the Office alleges (1) the helper peptide is

"essential to the instant invention." The Office further alleges (2) that the genus of helper peptides may not be defined by a single feature, i.e., an isoelectric point (pI), but must be defined by structure. The Office specifically alleges that the genus must be described by the amino acid sequence of the helper peptides, even if the artisan can determine the pI of the helper peptide. The Office further alleges (3) that the genus is so large and diverse that three examples of helper peptides do not provide sufficient written description of the genus. Applicants respond to these allegations in order.

(1)

To satisfy the written description requirement, the applicant must convey to the skilled artisan that, as of the filing date sought, the applicant was in possession of the invention. *See Falkner v. Inglis*, 448 F.3d 1357, 1365, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006). Compliance with the written description requirement is determined irrespective of whether a feature of the claims is "essential" to the invention, so this line of inquiry is irrelevant.

(2)

It is well established that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.' " *Enzo Biochem Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, 1615 (Fed. Cir. 2002) (citing with approval Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001), Example 9 at 35-37) (emphasis in original).

In the present case, the genus of helper peptides is not defined solely by the pI of the polypeptide, as the Office alleges. Claim 54, subsection (b), for example, recites that the helper peptide (i) has "a different isoelectric point [from the protective peptide and the peptide of interest] prior to use in said fusion protein"; (ii) "has 5 to 50 amino acid residues"; and (iii) "is designed so that the isoelectric point of the peptide of interest connected to a helper peptide is between 8 and 12."

The pI of a polypeptide, like its molecular weight, is a characteristic property that follows from the polypeptide's constituent amino acids. *See, e.g.*, MOLECULAR BIOLOGY OF THE CELL, Alberts *et al.*, eds., Garland Publishing, Inc., New York, 1983, pages 175 (emphasis in original):

> At a pH that is characteristic for each protein, there exists an *isoelectric point* at which the protein has no net charge and therefore will not migrate in an electric filed. In isoelectric focusing, . . . [e]ach protein moves to the position in the [pH] gradient that corresponds to it isoelectric point and stays there.

Further, the pI can be calculated routinely and predictably from a knowledge of only the constituent amino acids of a polypeptide. *See, e.g.*, California State University, "Calculation of pI for a Polypeptide," *at* http://wwwchem.csustan.edu/chem4400/pppI.htm (last accessed July 14, 2008), attached hereto as **Exhibit 2**. It reasonably follows that the skilled artisan routinely could predict the pI of a polypeptide having ***any combination*** of constituent amino acids.

The relevant functional characteristics of the recited helper peptide relate to its length and pI. *See, e.g.*, Specification, page 10, lines 16-33. Both of these functional characteristics follow directly from the amino acid sequence of the helper peptide. Using routine methods well known in the art, such as described above, the skilled artisan could predict *a priori* the pI of any fusion polypeptide from its amino acid sequence. The specification provides the requisite functional characteristics of helper peptides, coupled with a known correlation between function and structure. The claims thus comply with the Federal Circuit's relevant test for written description. *See, e.g.*, *Enzo*, 63 U.S.P.Q.2d at 1615. The rejection accordingly should be withdrawn.

In this context, the Examiner alleges that additional structure, particularly an amino acid sequence, of the helper peptide is required to comply with the written description requirement. To the contrary, the Federal Circuit explicitly states that a "complete structure" of a compound is ***not*** necessary for compliance with the written description of a compound, even in a relatively unpredictable art. *See, e.g.*, *Enzo*, 63 U.S.P.Q.2d at 1615. The Examiner presents no reason why, in light of the considerable scientific and technologic knowledge already in existence, additional description is required to comply with the written description requirement. *See Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005) ("The descriptive

text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.").

(3)

The Examiner alleges that three working examples of the claimed invention provide insufficient description of the genus of helper peptides. The Examiner relies implicitly on the holding in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997). The Federal Circuit held that a genus of DNAs may not be defined solely by a statement of function or result, where the recitation conveyed no distinguishing information about the identity of the claimed DNA sequences, such as their relevant structural or physical characteristics. *Eli Lilly*, 119 F.3d at 1568. The court instead held that a genus of DNA sequences may be described by disclosing a representative number of species within the genus. *Eli Lilly*, 119 F.3d at 1569. The Federal Circuit, however, has made it abundantly clear in subsequent decisions that this is ***not the only way*** a genus of biomolecules can be described. *See, e.g., Enzo*, 63 U.S.P.Q.2d at 1615; *Falkner v. Inglis*, 79 U.S.P.Q.2d 1001, 1007 (Fed. Cir. 2006) ("examples are not necessary to support the adequacy of a written description"). In the present case, for the reasons detailed above, the recitation of helper peptides ***does*** convey distinguishing information about the identity of the claimed helper peptides, such as their relevant structural or physical characteristics. For this reason, the Examiner's implicit reliance on *Eli Lilly* in this case is inapt. The rejection accordingly should be withdrawn.

7. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 54-62, 64-68, 72, 76, 78-81, 94-96, and 98 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a process of making the fusion proteins disclosed in the Figures, allegedly does not enable a process of making all fusion proteins within the scope of the claims. Applicants traverse the rejection.

The Examiner maintains the rejection on the grounds that "there is a countless number of [helper] peptides that consist of 5-50 amino acids and have the range of pI between 8 and 12" and that the "specification provides no guidance as to which of them will be useful in the instant invention." The recited genus of helper peptides is certainly very large, although not "countless." Determining the scope of the claims, however, is only the first step in a proper analysis of enablement. *See* MPEP § 2164.08, "Enablement Commensurate in Scope With

the Claims." For the following reasons, the specification enables a process of using a number of helper peptides reasonably commensurate with the scope of the claims.

In the present case, the specification teaches that all polypeptides having the recited characteristics of a helper peptide may be used in the recited process. *See, e.g.*, Specification, page 10, lines 16-33. The Office's burden is to provide reasons or evidence why the skilled artisan would doubt this conclusion. *See In re Cortright*, 165 F.3d 1353, 1357, 49 U.S.P.Q.2d 1464 (Fed. Cir. 1999). The Examiner points out that the genus of polypeptides encompassed by helper peptides is large, but if a reasonable number of the encompassed species work in the claimed process, then there is no reason to question whether the entire genus of helper peptides is enabled. *See, e.g., In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

The Examiner further states that the fusion between a helper peptide and a peptide of interest "would change characteristics of the peptide of interest." Applicants fail to understand why the Examiner cites an advantage of the claimed process as a ground for non-enablement. In fact, the helper peptide alters the physiochemical properties of the peptide of interest to circumvent problems in purifying and/or modifying the peptide of interest. *See, e.g.*, Specification, page 3, line 26, through page 5, line 4 (outlining problems known in the art with respect to purifying and/or modifying peptides of interest); page 9, line 36, through page 10, line 15 (disclosing how the helper peptide resolves these problems). The recited helper peptides have 5 to 50 amino acid residues and are designed so that the isoelectric point of the peptide of interest connected to a helper peptide is between 8 and 12. Further, the recited protective peptide, peptide of interest, and helper peptide each have a different isoelectric point prior to use in the fusion protein. The recited genus of helper peptides reasonably corresponds in scope to the helper peptides described in the specification as useful for carrying out the claimed process. In addition, the specification provides at least three working examples of the claimed process, as the Examiner admits. Given the ability of the skilled artisan to predict routinely the pI of a polypeptide, the specification provides a disclosure reasonably commensurate with the scope of the claimed process. Nothing more is required for enablement. *See, e.g., In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

The Examiner finally alleges that "the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable." Even if this unsupported statement were generally true, the Examiner does not explain why tertiary structure is relevant to the claimed process. For the reasons set forth above, the skilled artisan easily and routinely could predict *a priori* the pI of polypeptides. A considerable amount of experimentation is permissible, if it is merely routine in nature. *See* MPEP § 2164.06, "Quantity of Experimentation."

For all the reasons above, the experimentation required to practice the claimed process is not undue in nature, and the rejection accordingly should be withdrawn.

8. Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 54-62, 64-68, 72, 73, 76, 78-81, 94-96, and 98 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants traverse the rejection.

The Examiner apparently alleges that the skilled artisan would not understand what is meant by "alanine at position 8 of GLP-1," for example. It is well established that "the definiteness of the language employed must be analyzed—not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore* , 439 F.2d 1232, 1235, 169 U.S.P.Q. 236, 238 (C.C.P.A. 1971). The skilled artisan knows the sequence of GLP-1 and knows the position number of each residue in GLP-1. The claims are definite, when read in light of the specification and teachings of the prior art, and the rejection accordingly should be withdrawn.

Claims 70 and 71 are rejected as depending on a canceled claim. The present amendment moots this ground of rejection.

9. Claim Rejections under 35 U.S.C. § 102(e)

Claims 72, 73, and 76 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,891,671 ("Suzuki"). Applicants traverse the rejection.

The Examiner maintains the rejection on the basis that a "helper peptide" is synonymous with the "linker site" of Suzuki. The Examiner then alleges that "a peptide bond between the protective peptide and the linker can be cleaved by some agent, either a protease or a chemical agent, and therefore is a cleavage site." During prosecution, an examiner gives

claims their broadest reasonable interpretation in light of the specification as it would be interpreted by one of ordinary skill in the art. *See In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004). The Examiner's interpretation of any peptide bond as a cleavage site is unreasonable in light of the specification. Representative cleavage sites are described in the present specification at page 15, line 12, through page 17, line 20, for example. In light of the specification, the skilled artisan would not interpret a "cleavage site" as any peptide bond.

As Applicants pointed out before, the '671 patent at best teaches a fusion protein comprising [protective peptide]-[linker site]-[peptide of interest]. Applicants' claims are directed to a fusion protein generally described as [protective peptide]-[helper peptide]-[peptide of interest]. No linker site is recited in the composition of the pending claims. Additionally, the '671 patent does not teach or suggest the use of a helper peptide, let alone the order provided. The Examiner alleges otherwise based only on an unreasonable interpretation of a "cleavage site." Because the cited art does not teach each and every element of the claimed process, the rejection is improper and should be withdrawn.

10. Allowable Subject Matter

Applicants note that Claims 82 and 83 are objected to as being dependent upon are rejected base claim, but otherwise would be allowable if rewritten in independent form.

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CONCLUSION

In conclusion, this is believed to be in full response to the outstanding restriction requirement. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience. Should any outstanding fees be owed or overpayments credited, the Commissioner is invited to charge or credit Deposit Account No. 50-0573.

Respectfully submitted,
DRINKER, BIDDLE & REATH LLP

Date: July 16, 2008

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EXHIBIT 1

Abstract of CN 1167155
and
Courtesy copy of PTO Form 1449

Method for cleaving chimeric protein using processing enzyme

Publication number: CN1167155
Publication date: 1997-12-10
Inventor: SUZUKI YUJI (JP); MAGOTA KOJI (JP); MASUDA TOYOFUMI (JP)
Applicant: SUNTORY LTD (JP)
Classification:
- international: ***C07K14/585; C07K14/635; C12N1/21; C12N9/38; C12N15/62;*** **C07K14/435; C12N1/21; C12N9/38; C12N15/62;** (IPC1-7): C12P21/02; C12N15/63; C12P21/06
- European: C07K14/585; C07K14/635; C12N9/38; C12N15/62
Application number: CN19971009693 19970304
Priority number(s): JP19960070906 19960304

Also published as:

EP0794255 (A2)
US5891671 (A1)
EP0794255 (A3)
CA2198966 (A1)
EP0794255 (B1)

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Abstract not available for CN1167155
Abstract of corresponding document: **EP0794255**

A chimeric protein is provided which comprises a target protein and has been designed so as to be easily cleaved by a processing enzyme, permitting a target protein to be efficiently recovered. The chimeric protein is represented by the following formula: A-L-B wherein A represents a protective peptide; B represents a target peptide; and L represents a linker peptide having the sequence X1-X2-(Pro, Lys, or Arg)-Arg, wherein X1 and X2 represent any amino acid, in its C-terminal region and a domain rich in His in its N-terminal region.

A-L-B

INFORMATION DISCLOSURE CITATION	Attorney Docket No.: 47259-0373-00-US	Serial No.: 09/402,093
(Use several sheets if necessary)	Applicants Kazuhiro OHSUYE et al.	Page 1 of 1
PTO Form 1449	Filing Date: September 29, 1999	Group Art Unit: 1652

U.S. PATENT DOCUMENTS

*Examiner Initial		Document Number	Date	Name	Class	Sub Class	Filing Date

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Sub Class	Translation YES	NO
		1167155		CN			X (Abstract)	

OTHER DOCUMENTS

(Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.)

Examiner	Date Considered

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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EXHIBIT 2

California State University, "Calculation of pI for a Polypeptide," *at* http://wwwchem.csustan.edu/chem4400/pppI.htm (last accessed July 14, 2008).

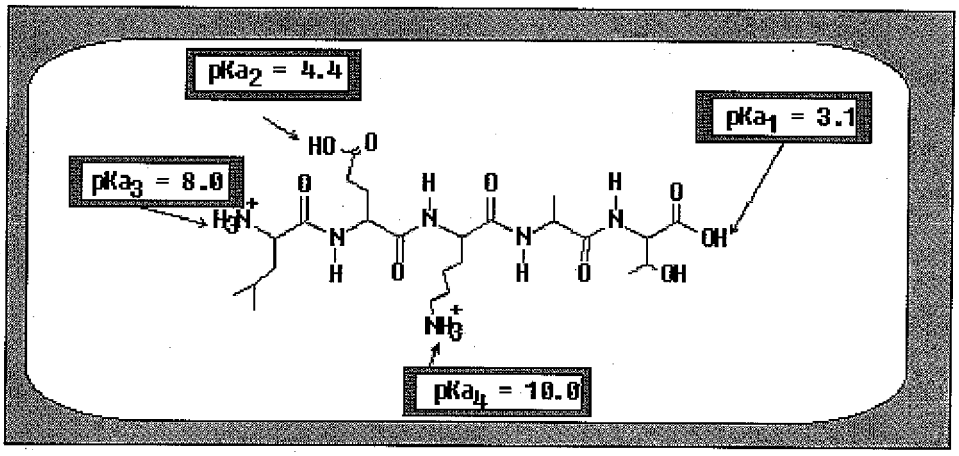
Calculation of pI for a Polypeptide.

The pI is the pH where the molecule exists in an uncharged state. Here are some practice problems for calculating the pI of a polypeptide.

1. What is the pI of LEKAT?

Answer:
The amino acids are:
leucine-glutamate-lysine-alanine-threonine
The pKa values are as follows:

- pKa_1 (carboxyl terminal)= 3.1
- pKa_2 (glutamate side chain) = 4.4
- pKa_3 (amino terminal) = 8--note that it is different when in a polypeptide.
- pKa_4 (lysine amino group) = 10.0



At the pI the net charge of the molecule is zero. To find the uncharged molecule, first figure out what the charge on the polypeptide is after the loss of each proton.

1. Below pH 2, the charge is +2
2. As base is added the first proton is removed from the terminal carboxyl group and the charge on the polypeptide is now +1.
3. As the pH is increased to 6.4 (two pH units above pKa_2) the second proton is removed and the charge on the polypeptide is now 0.
4. As the pH is increased to 10 (two pH units above pKa_3) the third proton is removed and the charge on the molecule is -1.
5. As the pH is increased to 12 (two pH units above pKa_4) the forth proton is removed and the charge on the molecule is -2.

To find the pI, average the two pKa values on either side of the neutral form of the polypeptide.

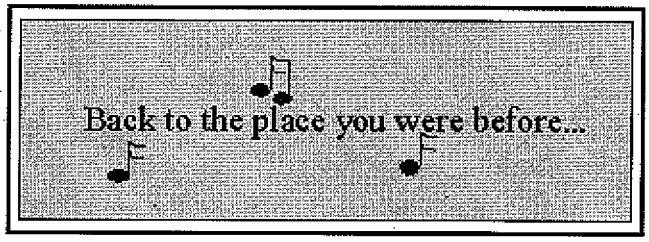
- $(pKa_2 + pKa_3)/2 = pI$
- $(4.4 + 8.0)/2 = 6.2$

Draw out the titration curve for LEKAT to convince yourself that the uncharged form is predominant at this pH.

For more practice:

1. What is the pI of the polypeptide GATHER?
2. What is the pI of the polypeptide HERE?

Be sure that you can predict the charge on a polypeptide at any pH. Remember that when the pH is two units above the pKa, the proton is gone. (Recall that pH is a negative log function, an increase of two units corresponds to the addition of **100** times **more** base.)



This returns you to the Biochemistry I page.
This page was written by Koni Stone, please send comments to koni@chem.csustan.edu